REMARKS

The undersigned attorney for applicant has filed a Power of Attorney from Orexo AB (the owner of the application) along with a Statement Under 37 C.F.R. 3.73(b).

I. Summary of Prior Proceedings

The Office Action mailed February 8, 2008, which was designated as being final, rejected the then-pending claims 1 to 38; 41; 42; and 46 to 86 under 35 U.S.C. § 103(a) based upon the combined disclosures of Saslawski (WO 99/33448 or, in shorthand, "the '448 patent") in view of Hedenström et al. (Ailment Pharmacol. Ther. 1997; 11:1137-1141). The then-pending claims 1; 40; 42; 45 to 48; 52; 71; 73; and 78 were also rejected under 35 U.S.C. § 103(a) based upon the combined disclosures of Saslawski (the '448 Patent); Hedenström; and Gschwantler et al (Ailment Pharmacol. Ther. 1999; 13:1063-1069). The then-pending claims 30 to 38; 41; 42; and 44 to 86 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting based upon then-pending claims 49 to 110 of co-pending Patent Application Serial No. 11/544,750.

For the record, Applicant restates portions of the Office's *Graham* "findings of fact" set forth in the Office Action. Restating the findings of fact provides a context for applicant's response in this Amendment (which is filed with a Request for Continued Examination).[1]

The Office's findings of fact, in pertinent part, are:

(O1) "The '448 Patent discloses a multi-layer formulation comprising multiple agents such as rantidine, famotidine, and omeprazole (page 7, lines 10 to 15)."

(O2) In the '448 Patent, "the drugs are present in separate layers where the first outer layer provides an immediate release and the second inner layer provides a prolonged sustained release of the active agent (abstract). The inner layer can be in the form of a core while the outer layer is a matrix in which the second drug is dispersed (abstract)."

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[1] "When making an obviousness rejection, Office personnel must therefore ensure the written record includes findings of fact concerning the state of the art and teaching of the references applied." MPEP 2141 Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103, Section II (Office Personnel as Factfinders), p. 2100-116.

"Once Office personnel have established the Graham factual findings and concluded that the claimed invention would have been obvious, the burden then shifts to the applicant to (A) show that the Office erred in these findings or (B) provide other evidence to show that the claimed subject matter would have been nonobvious." MPEP 2141 Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103, Section IV (Applicant's Reply), p. 2100-119)

(O3) "The resulting formulation dissolves in gastric juices (examples)."

(O4) "Regarding the claims which recite the limitation that the dosage form is capable of raising the gastric pH above 4, it is the position of the Examiner that such a limitation would be inherently met by the formulation of the since the dosage forms comprise high doses of active agents including proton pump inhibitors. This is evidenced by the **Hedenström** study, which discloses 2 hours after administration the gastric pH had risen above 4 for dosages of ranitidine and famotidine (figure 1). Any composition comprising at least the amounts of the compounds would also raise the gastric pH, The dosage forms were each fast acting easily administered. From this study a skilled artisan would see that fats (sic) acting H2 receptor agonists would inherently raise the gastric pH above 4 within 2 hours of administration."

(O5) "With these aspects in mind it would have been obvious to follow the suggestions and teachings of the '448 patent in order to produce a stable tablet for instant and prolonged release of compounds useful in treating GERD as described in the **Hedenström**. The formulation could be effervescent with the inclusion of the alkali compound and become dispersed in water for deliver (sic). One of ordinary skill in the art would have been motivated to follow these teachings and suggestions with an expected result of a stable biphasic release tablet.

(06) "Regarding arguments a. and b.,[2] it remains the position of the Examiner that the combination of the '448 patent with the **H. Hedenström** and **M. Gschwantler** studies provides methods for treating various infections and or gastro-intestinal disorders. Firstly the '448 patent teaches a bilayered dosage form comprising the prolonged release and immediate release of two separate active agents. Included in these active agents include proton pump inhibitors such as omeprazole and H2 receptor agonists such as cimetidine, ranitidine and famotidine (page 7, lin. 10-12). The dosage from comprises disintegrants, and other excipients useful in the controlled release of the dosage form. The dosage form of the '448 patent discloses each of the physical parameters of the instant claims. The patent establishes the functional equivalency of omeprazole, ranitidine,

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[2] Applicant's arguments filed October 9, 2007 were: (a) At the time of the invention there would have been no motivation to combine an H2 receptor antagonist with a proton pump inhibitor, and (b) The '448 patent does not obviate the instant invention since the two active agents are the same active ingredient, and therefor would not provide a composition combining an H2 receptor antagonist and a proton pump inhibitor.

famotidine and nizatidine, while the **H. Hedenström** study establishes that these compounds are useful for treating the same symptoms in different ways. The study establishes that omeprazole should be released over an extended period of time for best long term effects, while the ranitidine and famotidine can be released immediately for best effects. Also the study established that the slow acting omeprazole should be combined with another more immediately acting compound in order to treat to effect (treat immediate symptoms as they arise). Taken together it would have been obvious at the time of the invention to provides a combined dosage from to treat immediate symptoms of GERD and provide for prolonged disorder treatment. Applicant argues that the '448 patent teaches away from the instant invention by disclosing an embodiment where both active agents are the same. However Applicant is directed to the proceeding paragraph where the patent clearly discloses that the first and second may contain a different active ingredient (page 4, lin. 12-14). This disclosure taken with the further teachings of the patent (the excipients and specific active agents to combined and released) along with the teachings of the **H. Hedenström** study it remains the position of the Examiner that the combination obviates the claims."

After the Office Action, Applicant was granted a personal interview on April 25, 2008 with the Examiner and his Supervisor, whose time and attention are appreciated. At the interview, applicant submitted arguments to establish the level of skill in the art at the time of filing, and that the prevailing knowledge of the art would teach away from the combination of a PPI (a proton pump inhibitor) and a H2RA (H2 receptor antagonist). At the conclusion of the interview, the Examiner suggested the inclusion of the specific PPI and H2RA into the base claim. The Examiner also suggested the submission of Declarations "with strong language" supporting the level of skill in the art. The Examiner indicated that all declarations and amendments would be entered upon receipt.

II. The Amended Claims

Applicant seeks to focus, simplify, and advance prosecution in accordance with the Examiner's suggestions. To this end, applicant has amended independent claim 49; canceled claims 1 to 38; 41; 42 to 48; and 50 to 86 (claims 39; 40; and 43 were previously cancelled); and added new dependent claims 87 to 117. The amendment has reduced the number of pending claims from eighty-three (83) to thirty-two (32).

Following this amendment, claims 49 and 87 to 117 remain in the application. Of these, claim 49 is the sole independent method claim.

Sole independent claim 49 (as amended) defines a method for treating on demand at least one symptom of gastro-esophageal reflux disease (GERD) (for support, see, e.g., on Specification, p. 10, lines 1 to 7).

The method comprises identifying a proton pump inhibitor or a salt thereof (PPI) selected from a group consisting essentially of acid-activated agents that inhibit the gastric H+,K+-ATPase enzyme (for support, see, e.g., Specification, p. 8, line 23, to p. 9, line 8), and identifying an H2 receptor antagonist or a salt therefore (H2RA) selected from a group consisting essentially of agents that inhibit action of histamine on H2 receptors on parietal cell surfaces (for support, see, e.g., Specification, p. 9, lines 10 to 17; and p. 13, lines 31 to 33).

The method further comprises adopting an oral dose regime comprising selecting an oral dosage form for the H2RA for release of H2RA in the gastro-intestinal tract; selecting an oral dosage form for the PPI for release of PPI in the gastro-intestinal tract and that, when orally administered to the gastro-intestinal tract concomitantly with the H2RA, delays and/or extends the release of the PPI relative to the release of the H2RA, and orally administering concomitantly the selected oral dosage forms of the H2RA and the PPI to affect a rise in gastric pH to above about 3 within about 2 hours of administration. (for support, see, e.g., Specification, p. 14, lines 23 to 26) and Specification, p. 13, lines 15 to 24).

The method further comprises on demand, based upon an occurrence of at least one symptom of GERD, orally administering the selected oral dosage forms of the PPI and the H2RA concomitantly according to the dose regime to affect a rise in gastric pH to above about 3 within about 2 hours of administration, thereby treating at least one symptom of GERD promptly (for support, see, e.g., Specification, p. 13, lines 15 to 24; and p. 25, lines 1 to 6).

The method further comprises repeating the oral administration on demand, based upon a subsequent occurrence of at least one symptom of GERD, if necessary over a prolonged period (for support, see, e.g., Specification, p. 10, lines 1 to 7; and p. 19, lines 20 to 28). The use of the terminology "if necessary" is consistent with the on demand nature of the therapy as defined. If there is not a subsequent occurrence of a symptom, then a repeat of the oral administration is not necessary.

III. Applicant's Rebuttal

Applicant's rebuttal is organized into topical sections. These topical sections are listed at the outset, to help orient and guide the Examiner, as follows:

The Elements of Proof

Applicant accepts the burden of proving that the Office has erred in its *Graham* "findings of fact" O1 to O6 stated above. The claims have been amended to further emphasize the differences between the claimed subject matter and the prior art. Applicant will provide evidence to show that the claimed subject matter would not have been obvious at a time prior to when the invention was

made. For the purposes of these discussions, applicant notes that the subject matter of the amended claims has the benefit of a date of invention of at least October 16, 2002 (the foreign application priority date).

As the Examiner is aware, the consideration of obviousness is fact-driven as well as context-driven. It is fact-driven in that one needs to assess the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art, and resolve the level of ordinary skill in the art. (MPEP, 2141 Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103, Section II (The Basic Factual Inquiries of *Graham v. John Deere Co.*, p. 2100-116 to 118). It is context-driven in that, when making a determination of obviousness, the focus is on what a person of ordinary skill in the pertinent art would have known at a time prior to when the invention was made, and on what such a person would have reasonably expected to have been able to do in view of that knowledge (MPEP 2100-117). In shorthand, applicant will hereafter call the period of time prior to when the invention was made the "Relevant Time Period."

The Level of Ordinary Skill in the Art During the Relevant Time Period

The Office's findings of fact do not explicitly identify the level of ordinary skill in the pertinent art, nor do they identify the qualities of a person of ordinary skill in this art during the Relevant Time Period. For the purpose of rebutting the Office's findings, applicant identifies a person of ordinary skill in the art pertaining to the invention to be an individual, such as a physician (MD), college educator, or PhD scientist (e.g., a pharmacologist), who by virtue of personal and professional experience and expertise is knowledgeable in the field of gastroenterology and the pharmacological treatment of the disease called gastro-esophageal reflux disease (GERD). Such a person would be reasonably expected to know the contents of peer-reviewed literature pertaining to the physiology of gastric secretion and the treatment of GERD, and would also be reasonably expected to be mindful of the Hippocratic code for the ethical practice of medicine, including the tenet: "I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone." (emphasis added).

Summary of Proof

A core underpinning of the Office's factual findings is a presumption that the '448 patent would have suggested to a person of ordinary skill in the art during the Relevant Time Period to combine an H2RA (such as rantidine or famotidine) with a PPI (such as omeprazole) for administration to an individual suffering the symptoms of GERD. Applicant respectfully rebuts this presumption and the findings based upon it, and will demonstrate why.

When viewed from the perspective of a person of ordinary skill in the art during the Relevant Time Period, the '448 patent lists hundreds of known "active substances" across a broad spectrum of medicinal classes and indications. The '448 patent does not fairly teach or suggest the selection of any particular combination or combinations out of the infinite combinations that are theoretically possible. There is nothing in the "laundry list" of hundreds of known substances in the '448 patent that, absent knowledge and appreciation of the invention (i.e., hindsight), fairly leads a person of ordinary skill in the art to the selection of a PPI, the selection of a H2RA, and their co-administration according to an adopted dose regime in the manner defined in the amended claims.

The legal conclusion of obviousness requires "some articulated reasoning with some rational underpinning," such as combining prior art elements according to known methods to yield predictable results, or choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success (MPEP 2100-119, citing *KSR International Co. v. Teleflex, Inc.*, 82 USPQ2d at 1396). The Office's factual findings have, when viewed by a person of skill in the art during the Relevant Time Period, no requisite rational underpinning. In point of fact, the Office's findings would have been, when viewed by a person of skill in the art during the Relevant Time Period, scientifically illogical and fraught with a reasonable expectation of failure, and actual harm, to a human patient.

In rebuttal, the applicant submits the following findings of fact. The findings demonstrate, from the perspective of a person of ordinary skill in the art during the Relevant Time Period, with reference to contemporaneous, published peer-reviewed literature, what a person of skill in the art would be reasonably expected to know about matters pertaining to the invention as a whole, such as the physiological mechanism by which gastric (hydrochloric acid) is secreted by the stomach, the physiology of gastro-esophageal reflux disease (GERD) itself, and the separate, mutually exclusive usage of PPIs and H2RAs at that time by practitioners to treat the symptoms of GERD, as well as

what such a person would have been reasonably expected to do in view of that knowledge at the time.

When these matters are considered in an objective, straightforward way from the perspective of a person of ordinary skill in the art, it becomes apparent that, during the Relevant Time Period, the concomitant co-administration of a PPI and a H2RA was something a person of ordinary skill in the art would not do, because (a) based upon the known physiology and biochemistry of gastric acid secretion in the stomach, such co-administration of a PPI and a H2RA made no sense; (b) based upon the peer literature, such co-administration of PPI and H2RA was never appropriate; and (c) based upon animal data, such co-administration could reasonably be expected to be detrimental, not therapeutic.

Considered together, applicant's findings establish the facts and the context that lead to the conclusion that the invention as defined in the amended claims would not have been obvious.

Findings of Fact A1 to A5

The Physiology of Gastric Acid Secretion

Stimulation of Parietal Cells and The Proton Pump

A1. During the Relevant Time Period, persons of skill in the art understood the remarkable mechanisms by which gastric (hydrochloric) acid is secreted in the stomach. Writing in 2000, Drs. Wolfe and Sachs remark (see, Wolfe and Sachs, "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31 at S9):[3]

> "One of the hallmarks of the mammalian stomach is its ability to secrete large quantities of concentrated (0.16 mol/L) hydrochloric acid."

A2. During the Relevant Time Period, persons of skill in the art understood that specialized epithelium cells in a stomach (called parietal cells, which number about 1 billion in a normal human stomach) secrete gastric acid, which comprises hydrogen H+ ions (protons) in the form of concentrated hydrochloric acid. Hydrochloric acid plays a significant role in protein hydrolysis and other aspects of the digestive process. Hydrochloric acid also sustains a sterile intragastric environment. (see, Wolfe and Sachs, "Acid Suppression: Optimizing Therapy for

[3] / Copies of the documents that are cited in Applicant's Findings of Fact are found in the Information Disclosure Statement (Group 3) that accompanies this Amendment.

Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31 at S9).

A3. During the Relevant Time Period, persons of skill in the art understood the remarkable, complex biochemical reactions occurring in partial cells that create and secrete hydrochloric acid in the stomach. They understood that parietal cells possess the gastric enzyme -- hydrogen potassium –adenosine triphosphate (ATPase), or in shorthand. "H+/K+ ATPase" which drives the biochemical pump (the "proton pump") by which hydrogen H+ ions are secreted by parietal cells.. (see, Wolfe and Sachs, "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31 at S10, Figure 1, and S13).

A4. Persons of skill in the art during the Relevant Time Period understood that, when a person eats something or thinks about eating something, histamine (an organic molecule) is produced from amino acids by enterochromaffin-like cells (ECL cells) found in the gastric glands of the gastric mucosa beneath the epithelium, particularly in the vicinity of parietal cells. Special regions of the parietal cells (called H2 receptors) are stimulated by the histamine. Persons of skill in the art during the Relevant Time Period understood that the stimulation of the H2 receptors by histamine leads to a complex series of biochemical reactions, which ultimately leads to a conformational change in the H+/K+ ATPase enzyme that drives a transport of hydrogen ions (H+) out of the cytoplasm of the parietal cell into the secretory network of the parietal cell (called canaliculi), in exchange for potassium ions (K+). A person of ordinary skill in the art during the Relevant Time Period called this in-and-out exchange of potassium ions (K+) (in) for hydrogen ions (H+) (out) performed by parietal cells "a hydrogen ion or proton pump." A proton pump is not a pump in a mechanical sense, but a biochemical reaction occurring within a parietal cell due to a conformational change in the H+/K+ ATPase enzyme in response to histamine, which "pumps" out hydrogen ions H+ while sucking in potassium ions K+. (see, Wolfe and Sachs, "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31 at S9 to S12).

A5. Persons of skill in the art during the Relevant Time Period understood that the parietal cells also separately secrete chloride ions (Cl-) into the canaliculi by another biochemical process. Gastric acid enters the main stomach lumen. (see, Wolfe and Sachs, "Acid Suppression:

Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31, at S10, Figure 1).

Finding of Fact A6

The Physiology of GERD

A6. During the Relevant Time Period, persons of skill in the art also understood the morphology and physiology of gastroesophageal reflux disease (GERD). GERD is the presence of gastric acid in the esophagus, caused by abnormalities in the motor function in the lower esophagus and lower esophageal sphincter (LES) between the esophagus and the stomach. (see, Wolfe and Sachs, "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31 at S11). They understood that the regurgitation of hydrochloric acid from the stomach into the esophagus lead to painful and delibilitation symptoms – described at that time by a person of skill in the art (a medical doctor) as causing " more pain and greater impairment in social functioning and emotional well-being than patients with other chronic diseases such as diabetes and hypertension." During the Relevant Time Period, persons of skill in the art also understood successful treatment of GERD led to "marked improvement in the quality of life." Thus, persons of skill in the art at the time were incentivized to identify and use the best available treatment options for dealing with the symptoms of GERD. (see, Fass, Fennert, and Vakil, "Nonerosive Reflux Disease – Current Concepts and Dilemmas," American Journal of Gastroenterology, Vol. 96, No. 2, 2001:. 303-314 at. 309).

Findings of Fact A7 and A8

The Treatment of GERD

A7. During the Relevant Time Period, published peer-reviewed articles authored by persons of skill in the art recognized (see, Fass, Fennert, and Vakil, "Nonerosive Reflux Disease – Current Concepts and Dilemmas," American Journal of Gastroenterology, Vol. 96, No. 2, 2001 at 309):

> "There are numerous therapeutic options available for treating patients presenting with symptoms of GERD or otherwise suspected as having this disease. Generally these therapeutic options have been viewed in a hierarchy of therapeutic efficacy, ranging from lifestyle modifications/ antacids to histamine-2 receptor antagonists

(H2RAs)/prokinetics to proton pump inhibitors (PPIs), with surgery reserved for those with continued symptoms or complications of GERD (Citing an article published in 1994)."

A8. During the Relevant Time Period, persons of skill in the art recognized that antacids; H2RA's; and PPI's are distinctively different chemical agents, and that they work in distinctively different, and often incompatible ways (as will be explained below). (see, Wolfe and Sachs, "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31 at S16-19 and S-20-23).

Finding of Fact A9

How Antacids Function

Neutralization of Gastric Acid

A9. During the Relevant Time Period, persons of skill in the art understood that an antacid, by definition, is a chemical --- such as sodium bicarbonate, magnesium hydroxide, or aluminum hydroxide -- used to counteract or neutralize gastric acid in the stomach after it is secreted. What constitutes (and, conversely what does not constitute) an antacid was well known and identified at that time. Substances that were recognized by persons of skill in the art at that time to be antacids were listed in Title 21 U.S.C. § 331.11 (Food and Drugs) (1974). The absence of H2RA's and PPI's from this list means that, both scientifically and legally, H2RA's and PPI's were recognized by persons of skill in the art as not being antacids (pharmacologically, PPI and H2RA do not neutralize gastric acid after it is secreted, but work in altogether different biochemical ways at a cellular level, as will be described below). (see, Wolfe and Sachs, "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31, S20 to S23).

Finding of Fact A10

How H2RA's Function

Block Secretion of Gastric Acid: Prevent Stimulation of Parietal Cells

A10. During the Relevant Time Period, persons of skill in the art understood that H2RA's -- such as famotidine, ranitidine, and cimetidine -- are antisecretory agents. H2RA's do not neutralize gastric acid after it is secreted, but instead work systemically at a cellular level to block the

secretion of gastric acid by parietal cells in the first instance. H2RA's (delivered orally) enter the intestines, where they are absorbed into the blood and delivered systemically to parietal cells. In the parietal cells, H2RA's biochemically block the histamine H2 receptors on the parietal cell, to thereby prevent stimulation of the parietal cells and the initiation of the biochemical reaction (above described) that leads to the formation of a proton pump. If no proton pump forms, hydrogen ions H+ are not transported out of the parietal cells, so no gastric acid forms. This is the antisecretory pharmacologic effect of H2RA's known to persons of skill in the art during the Relevant Time Period. (see, Soll, "Gastric, Duodenal, and Stress Ulcer.," Gastrointestinal Disease, ed Sleisenger and Fordtran, (Fifth Edition), 1993 at. 619-630, p. 622) (see, Soll, "Gastric, Duodenal, and Stress Ulcer.," Gastrointestinal Disease, ed Sleisenger and Fordtran, (Sixth Edition), 1998 at. 646-649) (see, Wolfe and Sachs, "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31 at S12).

Finding of Fact A11

How PPI's Function

Block Secretion of Gastric Acid: Turning off the Proton Pump

A11. During the Relevant Time Period, persons of ordinary skill in the art understood that PPI's -- such as omeprazole, lansoprazole, and rabeprazole -- are also antisecretory agents. PPI's do not neutralize gastric acid after it is secreted. A person of ordinary skill in the art during the Relevant Time Period understood that PPI's, like H2RA's, perform at a cellular level to block the secretion of gastric acid by parietal cells. They also understood that PPI's (delivered orally), like H2RA's, are absorbed in the intestines and are delivered systemically to parietal cells. They further understood that PPI's are in function distinctly different than H2RA's. During the Relevant Time Period, persons of ordinary skill in the art understood that PPI's, in order to function, needed to be concentrated and activated in the acidic compartments of parietal cells that had been stimulated by histamine. Once activated in the acidic environment of the stimulated parietal cell, the PPI is chemically converted to another chemical form that binds irreversibly with the H+/K+ ATPase enzyme, thereby inactivating the H+/K+ ATPase enzyme. The activation of the PPI within the acidic environment of a parietal cell stimulated *inter alia* by histamine prevents the conformational change in the H+/K+ ATPase enzyme that creates the proton pump. In other words, the PPI

blocks the final pathway of acid secretion, by inactivating or tuning off the biochemical proton pump. When the proton pump is turned off, hydrogen ions H+ are not transported out of the parietal cells, so no gastric acid forms. This is the antisecretory pharmacologic effect of a PPI known to persons of skill in the art during the Relevant Time Period. (see, Soll, "Gastric, Duodenal, and Stress Ulcer.," Gastrointestinal Disease, ed Sleisenger and Fordtran, (Fifth Edition), 1993 pp. 619-630, at. 625) (see, Soll, "Gastric, Duodenal, and Stress Ulcer.," Gastrointestinal Disease, ed Sleisenger and Fordtran, (Sixth Edition), 1998, pp. 647-649) (see, Wolfe and Sachs, "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31. S13 to S15).

Finding of Fact A12

The Incompatible Biochemical Function of H2RA's and PPI

The Instruction: Do Not Co-Administer

A12. During the Relevant Time Period, persons of ordinary skill in the art understood that PPI's exerted their effect only as a consequence of the acidic environment in stimulated parietal cells (see, Soll, "Gastric, Duodenal, and Stress Ulcer.," Gastrointestinal Disease, ed Sleisenger and Fordtran, (Fifth Edition), 1993 at 626) (see, Soll, "Gastric, Duodenal, and Stress Ulcer.," Gastrointestinal Disease, ed Sleisenger and Fordtran, (Sixth Edition), 1998, at 649). In the absence of stimulation of the parietal cell for example by histamine, a PPI would not become activated and served no purpose. Further, during the Relevant Time Period, a leading textbook in the field of gastroenterology and other peer-reviewed articles look to the incompatible biochemical functions of PPI's and H2RA's within parietal cells, and citing animal (dog) data at the time, explicitly and repeatedly instruct persons of ordinary skill in the art not to co-administer PPI's and H2RA's to humans:

"Omeprazole (PPI) should not be co-administered with an other antisecretory agent." (see, Soll, "Gastric, Duodenal, and Stress Ulcer.," Gastrointestinal Disease, ed Sleisenger and Fordtran, (Fifth Edition), 1993, pp. 619-630.at 627).

"Combination therapy (of PPI's) with H2RAs is never appropriate ..." (see, Soll, "Gastric, Duodenal, and Stress Ulcer.," Gastrointestinal Disease, ed Sleisenger and Fordtran, (Sixth Edition), 1998 at. 649).

"The PPIs are without question the most potent inhibitors of gastric acid secretion available. However, because they are most effective when the parietal cells is stimulated to secrete acid in response to a meal, these drugs should *only* (emphasis in original text) be taken before or with a meal and should *not* (emphasis in original text) be used in conjunction with H2-receptor antagonists, postaglandins, or other antisecretory agents (see Table 3)" Table 3 (Helpful Facts on the Use of PPIs) further states: "Do *not* (emphasis in original text) administer concomitantly with H2-receptor antagonists or postaglandins." (see, Wolfe and Sachs, "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," Gastroenterology 2000; 118:S9-S31 at S14).

Finding of Fact A13

Hedenström and Gschwantler as Persons of Ordinary Skill in the Art

A13. Hedenström and Gschwantler are persons of ordinary skill in the art during the Relevant Time Period. The Hedenström article (published in 1997) and the Gschwantler article (published in 1999)[4] reflect the practice of persons of ordinary skill during the Relevant Time Period. Neither Hedenström nor Gschwantler co-administer PPI's and H2RA's. Both perform side by side single dose studies, where single dose PPI's are administered to one group of patients, and single dose H2RA's are administered to another group of patients. The results are then compared. Neither Hedenström nor Gschwantler suggest the administration of PPI or H2RA in any way except separately, either (a) as PPI, or (b) as H2RA.

Review of Findings of Fact A1 to A13

The foregoing factual findings A1 to A13 rebut the premise underpinning the Office's factual findings. A person of skill in the art during the Relevant Time Period would not select a PPI, select a H2RA, and co-administer them according to a dose regime, as defined in the amended claims. Based upon the preponderance of scientific evidence and understanding at the time as to how gastric acid is secreted **(A1 to A5)** and how PPI's and H2RA's function (**A10; A11**), it would be scientifically illogical to do so (**A12**). During the Relevant Time Period, a person of skill in the art understood that a PPI, to be effective needs to be activated, by way of a stimulated parietal cell **(A11;**

[4] / The Gschwantler article is directed to the treatment of *Helicobacter pylori* infection by the administration of antibiotics with a PPI, compared with the administration of antibiotics with an H2RA. The amended claims are directed to the treatment of GERD, not the treatment of *Helicobacter pylori* infection. Still, the Gschwantler article does reflect the practice of persons of ordinary skill in the art during the Relevant Time Period, which is germane to *Graham* analysis of the amended claims.

A12), and further understood that the administration of H2RA blocked the H2 receptors and thereby blocked stimulation of the parietal cell **(A10)**. That is to say, H2RA's switch off the very thing that PPI's need to exert their effect. Thus, during the Relevant Time Period, persons of ordinary skill in the art understood that the administration of a H2RA was incompatible with the administration of a PPI **(A12)**.

Not only was the co-administration of H2RA and PPI scientifically illogical to a person of ordinary skill in the art during the Relevant Time, but there were also explicit instructions in the peer-reviewed literature at the time not to do so (**A12**). There was no reasonable expectation during the Relevant Time Period that the co-administration of H2RA and PPI would lead to a successful result. Instead, animal data suggested that potential harm to humans could result (**A12**).

A person of ordinary skill in the art during the Relevant Time Period would understand the explicit and repeated teachings of the peer-reviewed literature, and would also be mindful of the Hippocratic code for the ethical practice of medicine -- to "Do no harm." Such a person would not select a PPI, select a H2RA, and co-administer them according to a dose regime under any condition. The '448 patent, Hedenström, and Gschwantler provide no independent rationale or incentive to do so (**A13**).

Hedenström concludes: (p. 1141, emphasis added)

"... single-dose administration of (PPI) had only a small effect on intragastric pH, as would be expected. At no time point was mean intragastric pH 3 or higher. Many patients with episodic symptoms of GERD take drugs only for symptom relief, when needed. Single-dose intake of (PPI) for symptomatic treatment is not an adequate way of administration. Continuous treatment with (PPI), i.e., repeated drug administration, is a prerequisite for an adequant response on intragastric pH."

Gschwantler concludes (p. 1067, emphasis added):

"Eridication regimens (for Helicobacter pylori) combining one or two antibiotics with a proton pump inhibitor have been studied intensively during the past few years. In contrast, only few studies have been focused on the possible role of H2-receoptor antagonists (H2-RA) in eradication therapy, and it is controversial whether substitution of the proton pump inhibitor with a H2-RA in an otherwise identical standard regime would yield similar results."

Neither Hedenström nor Gschwantler teach or suggest any way of administering PPI or H2RA except either (a) as a PPI, or (b) as a H2RA.

Hedenström represents the problems facing persons of skill in the art at the time the invention was made, and not the solution as defined in the amended claims. To exemplify the nature of the prior art problem solved by the invention, the applicant submits additional findings of fact:

Finding of Fact A14

The Shortcoming of Prior Art GERD Therapies (The Problem)

A14. The tradeoffs between providing H2RA therapy and providing PPI therapy in treating GERD, illustrated in Hedenström, were well known and recognized by persons of skill in the art during the Relevant Time Period. During the Relevant Time Period, the then-available treatment strategies involving H2RAs and PPIs were well described in the peer-reviewed literature (see, N. Vakil, "Review Article: Cost-Effectiveness of Different GERD Management Strategies," Aliment Pharmacol Ther 2002; 16 (Suppl. 4): 79-82, p. 80). The author (a person of skill in the art during the Relevant Period) concludes at that time:

> "Proton pump inhibitor therapy is more effective than H2 receptor antagonist therapy in erosive GERD."

Findings of Fact A15 and A16

Ineffectiveness of H2RA Therapy : No Prolonged Relief

A15. The peer-reviewed literature during the Relevant Time Period also describes a "step-up" therapy option used by the Veterans Administration because H2RA therapy proved ineffective (see, N. Vakil, "Review Article: Cost-Effectiveness of Different GERD Management Strategies," Aliment Pharmacol Ther 2002; 16 (Suppl. 4): 79-82, p. 80, citing an article published in 1999):

> "[The Veterans Administration] evaluated a strategy beginning with a generic H2-RA. Failures with this strategy would be treated with a higher dose of H2-RA therapy, and failures to the latter treated with proton pump inhibitors (step-up therapy)."

A16. In another article in 2000, a 1999 study was reported in which symptomatic GERD patients with an incomplete response to a three month therapy with a twice daily dose of H2RA, were subject to a further two months of continued therapy at a double dose of H2RA with only modest improvements compared to controls, leading the authors to note the "pharmacological deficiencies of H2RA's in controlling acid secretions" (see, Fass, Fennert, and Vakil, "Nonerosive

Reflux Disease – Current Concepts and Dilemmas," American Journal of Gastroenterology, Vol. 96, No. 2, 2001. pp. 309). In the same article, the authors also comment: "[H2RA] agents have been known to be ineffective in inhibiting meal-stimulated acid secretion and are associated with rapid development of pharmacological tolerance." The authors also cite data that "indicate overwhelmingly that, in patients with erosive esophagitis, PPI's provide superior healing and symptom relief compared to H2RA's ..." (p. 309-310).

Finding of Fact A17

Ineffectiveness of PPI Therapy: No Prompt Relief

A17. Persons of ordinary skill in the art also understood during the Relevant Time Period that PPI's, though superior to H2RA's in treating GERD, had their clinical shortcomings, too. First and foremost, there was a significant time lag (4 days) between the administration of PPI and the relief of the symptom. In contrast, H2RA therapy provided rapid relief, but it faded with time. With PPI, prompt relief was not possible, even at higher dosage levels, so the profound debilitating effects of GERD could not be promptly moderated, but came only with the passage of time. The shortcomings of PPI therapy in treating GERD were also well known and recognized in 2000. A leading textbook in the field of gastroenterology at the time, reflects upon these shortcomings (Soll, "Gastric, Duodenal, and Stress Ulcer.," Gastrointestinal Disease, ed Sleisenger and Fordtran, (Sixth Edition), 1998, p.. 648):

> "A time lag of about 4 days occurs before peak antisecretory effectively is achieved for PPI, probably reflecting progressive inhibition of the H-,K- -ATPase and possibly increases in bioavailability. This lag is inversely related to dose."

The textbook further counsels physicians interested in providing prompter relief to their patients:

> "Rapid control of acid secretion can be achieved using higher doses of a PPI, or more frequent administration (i.e., three or four doses of 20 mg of omeprazole in the first 24 hours),"
>
> and further remarks:
>
> "Combination therapy with H2RAs is never appropriate; if greater antisecretory efficacy is required, the PPI should be administered in higher, divided doses." (Ibid, p. 649).

Review of Findings of Fact A14 to A17

The foregoing factual findings A14 to A17 further rebut the Office's factual findings relating to the '488 patent, Hedenström, and Gschwantler. At a time prior to when the invention was made, physicians dedicated to the treatment of the profound and debilitating symptoms of GERD had at their disposal imperfect pharmacological tools (**A15; A16**). Hedenström and Gschwantler reflect this. The therapeutic tools that were available left the problem of rapid and prolonged relief from the symptoms of GERD unsolved. The conventional wisdom expressed in Hedenström and Gschwantler matched the understanding expressed in leading medical textbooks and held by other thought leaders in the field at this time. Persons of ordinary skill in the art at a time prior to when the invention was made advocated either (a) a H2RA therapy, or (b) a PPI therapy, or (a) an H2RA therapy and then (b) a PPI therapy (**A14; A15; A16**). Persons of ordinary skill in the art at a time prior to when the invention was made accepted that H2RA's provided prompt relief, but proved ineffective and had fading results in the longer term (**A15; A16**). This prompted persons of ordinary skill in the art at a time prior to when the invention was made to increase the H2RA dosage until the patient developed pharmacological tolerance to H2RA's, and the H2RA therapy ultimately failed to relieve the symptoms, even at higher dosages (**A15**). Ultimately, with H2RA therapy, the symptoms of GERD returned to disrupt the patient's quality of life. With PPI's, persons of ordinary skill in the art at a time prior to when the invention was made accepted the significant time lag of several days (**A17**), during which the patient continued to suffer the profound quality of life effects. The problem persisted during the time prior to when the invention was made: there was no therapy that made possible rapid and prolonged relief from the symptoms of GERD on demand. This is evidenced in published literature of the time authored and read by persons of ordinary skill in the gastroenterology field.

Differences Between the Amended Claims and Prior Art (The Solution)

The invention defined in amended claim 49 provides a treatment therapy for GERD in which identifies a PPI, identifies an H2RA, adopts an oral dose regime under which the PPI and H2RA are co-administered on demand concomitantly into a gastro-intestinal tract, either in a single dosage form or in separate dosage forms. Further, the therapy co-administers the PPI and H2RA on demand in a manner in which the release of the PPI in the gastro-intestinal tract is delayed and/or extended when compared to the release of the H2RA in the gastro-intestinal tract. Still

further, the therapy adopts a dosage regime that makes possible relief of symptoms of GERD on demand in a manner never before contemplated; namely, promptly – with a rise in gastric pH to above about 3 within about 2 hours of administration -- and which can be repeated on demand over a prolonged period without diminution of results.

In determining the differences between the prior art and the claims, the claimed invention must be viewed as a whole (MPEP, 2141.02).

(1) The invention defined in the amended claims treats at least one symptom of gastro-esophageal reflux disease (GERD) by co-administering the PPI and H2RA on demand in a manner in which the release of the PPI in the gastro-intestinal tract is delayed and/or extended when compared to the release of the H2RA in the gastro-intestinal tract.

The prior art does not teach or suggest co-administration of PPI and H2RA, much less in a oral dosage form that provides an intentional different rate of release of PPI relative to H2RA.

(2) The invention defined in the amended claims treats at least one symptom of gastro-esophageal reflux disease (GERD) by adopting a dose regime for the oral dosage by selecting a dosage forms for the PPI and the H2RA which delay and/or extend the release of PPI relative to the H2RA to affect, upon concomitant administration to the gastro-intestinal tract, a rise in gastric pH to above about 3 within about 2 hours of administration, and by on demand, based upon an occurrence of at least one symptom of GERD, orally administering the oral dosage form according to the dose regime, and by repeating the oral administration on demand, based upon a subsequent occurrence of at least one symptom of GERD, if necessary over a prolonged period.

The prior art does not teach or suggest co-administration of PPI and H2RA together, much less in a differentiated release form and also an "on demand" basis that provides a prompt rise in gastric pH to above about 3 within about 2 hours of administration over a prolonged period. The prior art teaches that the prompt relief provided by H2RA will fade over a prolonged period, as the body develops a tolerance to histamine blocking effects. The prior art also teaches that administration of a H2RA will cripple the intended effect of PPI, because H2RA block stimulation of the parietal cells essential for PPI activation. In neither instance does the prior art teach or suggest that a prompt and prolonged therapy as defined in the amended claims can be achieved in the manner defined in the claims.

Double Patenting Rejection

Responding to the Examiner's provisional rejection of the claims of the instant application (prior to amendment) on the grounds of nonstatutory obviousness-type double patenting based upon claims in co-pending Application Serial No. 11/544,750, applicant reports that the claims in the '750 application have also been amended in a response submitted on even date with the response in the instant application. Upon allowance of claims in either application, applicant will consider the merits of any of nonstatutory obviousness-type double patenting rejection.

Further Supplemental Evidence is Forthcoming

As further suggested by the Examiner, Applicant will in the near future supplement this response with the submission of declarations made by persons of skill in the art at a time prior to when the invention was made. An Interview Request will accompany the submission of the declarations. Applicant believes an interview prior to the examination of the amended claims would be helpful to the Examiner and would expedite prosecution of this application toward allowance.

IV. Related Applications

The Examiner's attention is directed to related co-pending applications Serial No. 10/475,254 and Serial No. 11/822,502 (the "Related Applications"). At the time the invention defined in the amended claims was made, the instant application and the Related Applications were owned by the same person (Orexo AB) under the provisions of 35 U.S.C. § 103(c), which therefore apply.

The Related Applications are undergoing examination by Examiner S. Tran (Art Group 1615). Examiner Tran has rejected claims directed to dosage forms comprising a PPI and a H2RA, and associated methods of treatment using the dosage forms, under 35 U.S.C. 103 based upon Coffin et al. WO 95/22320 in view of McGrew US 6,949,264 or Vertesy et al US 6,077,830 or Fuisz US 5,561,987 and Depui et al US 6,132,771.

Based upon the claims presented in the Related Application, the Examiner has made the following findings:

"Coffin teaches a solid dosage form comprising two populations of ranitidine (H2 receptor antagonist), an immediate release and a sustain release portions (abstract; and page 2). The immediate and sustained release portions are prepared separately and formulated into concentric, laminated tablet or mini tablet, or beads to be administered in a capsule (page 3, lines 17-22). Coffin

further teaches the addition of other active agent such as other H2 receptor antagonists, or antacids into both immediate and sustained release ranitidine portions of the dosage form (page 4, lines 17-25; and page 5).

"Coffin does not specifically teach other active including PPI.

"Vertesy teaches antacid includes omeprazole (column 11, lines 28-29).

"McGrew teaches antacid includes omeprazole (column 7, lines 32-33).

"Fuisz teaches an anti-ulcer agent includes cimetidine, ranitidine, nizatidine, famotidine, omeprazole, and mixture there of (claim 3).

"Thus, it would have been obvious to one of ordinary skill in the art to modify the dosage form of Coffin to include omeprazole as other active agent in combination with ranitidine to obtain the claimed invention. This is because Vertesy and McGrew teach that omeprazole is a well known antacid agent, because Vertesy teaches omeprazole is commonly known as an antacid agent useful for therapy and prophylaxis of gastric disorders (abstract; column 11, lines 28-29; and column 12, lines 25-48), because Fuisz teaches that combination of H2 receptor antagonist and omeprazole is known and useful for the treatment of disease associated with gastric ulcer (column 5, lines 40-48), and because Coffin teaches the desirability to combine ranitidine with other active agents to obtain an oral dosage form useful for the treatment of duodenal ulcers (page 1, lines 21¬25; and page 3, lines 1-5)."

Applicant rebuts the Examiner's findings in the Related Applicants for reasons that include: (i) a person of ordinary skill in the art understood at a time prior to when the invention was made that PPI's are not antacids (see above findings A8 to A12). Knowing this, a person of ordinary skill in the art would not interpret Coffin in view of McGrew or Vertesy in the manner proposed by the Examiner; and (ii) even if one accepts the Examiner's interpretation (which applicant does not), a person or ordinary skill in the art at a time the invention was made understood that the co-administration of H2RA and PPI was scientifically illogical, and was also faced with explicit instructions in the peer-reviewed literature at the time <u>not</u> to do so (see above findings A1 to A17); and further (iii) amended claim 49 is not before the Examiner in the Related Applications, so the Examiner has not had the opportunity in the Related Applications to consider the differences between the prior art and the subject matter defined in amended claim 49, when viewed as a whole, as have been presented in the instant application.

V. Information Disclosure Statement

The Examiner's attention is directed to the Supplemental Information Disclosure Statement that accompanies this Amendment. The Statement lists documents that have been categorized into three Groups for the convenience of the Examiner. The Statement cross cites into the instant application documents of record in the Related Applications (Group 1); lists documents that are referred to as background in the instant Specification, but that have not heretofore been made of record (Group 2); and list documents cited in applicant's findings of fact (Group 3). Copies of the documents in each Group accompany the Statement.

VI. Conclusion

Applicant believes that the record (as will be further supplemented) establishes that, taking into account the scope and content of the prior art, the differences between the claim invention and the prior art, and the level of ordinary skill in the art, the subject matter defined in amended claims 49 and 87 to 117 is not encompassed by the prior art.

Respectfully Submitted,

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